מרץ 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : <u>עדכוני בטיחות בעלוני התכשיר</u>
<u>Tafinlar 50 mg, 75 mg, Hard capsules</u>

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא ובעלון לצרכן של התכשירים **Tafinlar 50mg,** **Tafinlar 75mg.**

התוויות התכשיר:

<u>Melanoma</u>
Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
<u>Adjuvant treatment of melanoma</u>
Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
<u>Non-small cell lung cancer (NSCLC)</u>
Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.
<u>Anaplastic Thyroid Cancer (ATC)</u>
Dabrafenib is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

חומר פעיל:

DABRAFENIB (AS MESILATE) 50mg, 75mg

בהודעה זו מפורטים העדכונים המהווים עדכון במידע בטיחותי בלבד. למידע מלא יש לעיין בעלוני התכשיר.
העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום: נוברטיס ישראל בע"מ. תוצרת הארץ 6, ת.ד. 7126, תל אביב

העלון לרופא עודכן במרץ 2022, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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4.2 Posology and method of administration

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Dose modification

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~~Therapy should be interrupted if the patient's temperature is ≥38.5ºC. Patients should be evaluated for signs and symptoms of infection (see section 4.4).~~

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Table 2 Dose modification schedule based on the grade of any adverse events (AE) (excluding pyrexia)

Grade (CTC-AE)*	**Recommended dabrafenib dose modifications** Used as monotherapy or in combination with trametinib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

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Pyrexia
If a patient's temperature is ≥38°C therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4). Dabrafenib, or both dabrafenib and trametinib when used in combination, should be restarted if the patient is symptom free for at least 24 hours, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for ~~pyrexia~~, uveitis, RAS mutation positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

~~*Pyrexia*~~
~~When dabrafenib is used alone and in combination with trametinib, therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5°C (for dose modification guidance see Table 2). Trametinib should be continued at the same dose. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.~~

~~Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4).~~

~~Upon resolution of pyrexia dabrafenib should be restarted with appropriate anti-pyretic prophylaxis, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.~~

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4.4 Special warnings and precautions for use

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Pyrexia

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Therapy (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) ~~with dabrafenib~~ should be interrupted if the patient's temperature is ≥38.~~5~~°C (see section 5.1)~~(please refer to Table 2 for dose modification guidance)~~. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection.
Therapy~~Dabrafenib~~ can be restarted once the fever resolves ~~with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.~~
If fever is associated with other severe signs or symptoms, therapy~~dabrafenib~~ should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).
~~No dose modification of trametinib is required when taken in combination with dabrafenib.~~

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5.1 Pharmacodynamic properties

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Other studies - pyrexia management analysis
Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)
Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both medicinal products when patient's temperature is ≥38°C (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

העלון לצרכן עודכן במרץ 2021, להלן העדכונים המהווים עדכון במידע בטיחותי (החמרה במידע בטיחותי מודגשת בצהוב):

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2. לפני השימוש בתרופה

...

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חום

נטילת טפינלר או שילוב של טפינלר וטרמטיניב עלולה לגרום לחום, אם כי זה סביר יותר אם הנך לוקח את הטיפול המשולב (ראה גם סעיף 4). במקרים מסוימים, אנשים עם חום עלולים לפתח לחץ דם נמוך, סחרחורת או תסמינים אחרים. **ספר מיד לרופא שלך אם יש לך חום** מעל 38.5°C או אם אתה מרגיש שעומד לעלות לך החום בזמן שאתה לוקח תרופה זו.

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4. תופעות לוואי

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תופעות לוואי חמורות אפשריות

חום

נטילת טפינלר עלולה לגרום לחום ביותר ממשתמש אחד מ-10. **ספר לרופא שלך מיד אם אתה מפתח חום (טמפרטורה של 38.5°C או יותר) או אם אתה מרגיש שעומד לעלות לך החום בזמן שאתה לוקח תרופה זו.** הרופא יבצע בדיקות כדי לברר אם יש גורמים אחרים לחום ויטפל בבעיה.

במקרים מסוימים, אנשים עם חום גבוה עלולים לפתח לחץ דם נמוך וסחרחורת. אם החום חמור, הרופא שלך עשוי להמליץ שתפסיק לקחת טפינלר, או טפינלר וטרמטיניב, בזמן הטיפול בחום עם תרופות אחרות. ברגע שהחום יאוזן, הרופא שלך עשוי להמליץ שתתחיל לקחת טפינלר שוב.

...

בברכה,

אסתר תירוש
רוקחת ממונה

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